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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,617	05/03/2002	Audrey Goddard	P3230R1C001-168	4531

20995 7590 03/20/2006

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ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/20/2006

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/063,617
Filing Date: May 03, 2002
Appellant(s): GODDARD ET AL.

Anne Marie Kaiser
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/27/2005 appealing from the Office action mailed 07/26/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

Claims 14-17 are rejected under 35 U.S.C. § 112, first paragraph, because the scope of enablement provided to the skilled artisan by the disclosure is not commensurate with the scope of protection sought by the claims.

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Hu et al. Analysis of genomic and proteomic data using advanced literature mining. J Proteome Res. 2003 Jul-Aug;2(4):405-12.

Wang et al. mRNA differential display: application in the discovery of novel pharmacological targets. Trends Pharmacol Sci. 1996 Aug;17(8):276-9.

Haynes et al. Proteome analysis: biological assay or data archive? Electrophoresis. 1998 Aug;19(11):1862-71.

Hancock WS. Do we have enough biomarkers? J Proteome Res. 2004 Jul-Aug;3(4):685.

The declaration of Paul Polakis under 37 CFR 1.132 (Exhibit 6, filed 05/02/2005)

Molecular Biology of the Cell, 3rd edition (Exhibit 7, filed 05/02/2005)

Molecular Biology of the Cell, 4th edition (Exhibit 8, filed 05/02/2005)

Genes VI (Exhibit 9, filed 05/02/2005)

Meric et al. Translation initiation in cancer: a novel target for therapy. Mol Cancer Ther. 2002 Sep;1(11):971-9. (Exhibit 11, filed 05/02/2005)

Henikoff et al. Gene families: the taxonomy of protein paralogs and chimeras. Science. 1997 Oct 24;278(5338):609-14.

(9)(a) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 6-8 and 11-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to or encompass an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 110 (PRO1753) or comprising an amino acid sequence having a recited % identity thereto.

The specification discloses a nucleotide sequence (SEQ ID NO: 109) of a native sequence PRO1753 cDNA, wherein SEQ ID NO: 109 is a clone designated as "DNA68883-1691" (paragraph 0135). FIG. 110 shows the amino acid sequence (SEQ ID NO: 110) derived from the coding sequence of SEQ ID NO: 109 shown in FIG. 109 (paragraph 0136). The specification discloses uses for PRO polynucleotides and polypeptides in general (paragraphs 0316-0360; pages 86-100). Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution) discloses that DNA68883-1691 is more highly expressed in esophageal tumor as compared to normal esophagus (page 143).

The specification discloses that secreted proteins and membrane-bound proteins and receptors have widely varying activities (paragraphs 0002-0004). This finding establishes that

secreted proteins and membrane-bound proteins and receptors have very diverse functions and makes it clear that classification of a protein as a secreted protein or a membrane-bound protein or receptor does not identify it as having a specific function. The specification provides no basis for concluding which, if any, of the varied activities of secreted proteins and membrane-bound proteins and receptors is possessed by the PRO1753 polypeptide. There is no evidence that a skilled artisan would have appreciated the identification of the PRO1753 polypeptide, without more, would have suggested any specific patentable utility.

The disclosed uses for PRO polynucleotides and polypeptides in general (paragraphs 0316-0360) are not specific to the PRO1753 polypeptide.

Although the specification discloses that DNA68883-1691 is more highly expressed in esophageal tumor as compared to normal esophagus (page 143), the specification provides no information regarding the absolute values of the differences in transcript levels and provides no information regarding level of expression, activity, or role of the PRO1753 polypeptide in cancer. The skilled artisan would not know if the disclosed change in PRO1753 transcripts is tumor-dependent or tumor-independent. See Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12), which teaches:

> "[h]igh-throughput technologies, such as proteomic screening and DNA micro-arrays, produce vast amounts of data requiring comprehensive analytical methods to decipher the biologically relevant results" (Abstract).
>
> "In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (page 405, left column, full paragraph 1).
>
> "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful. ... For genes displaying a 5-fold change or less ... there was no evidence of a correlation between

> altered gene expression and a known role in the disease. This reflects ... genes whose modest changes in expression may be unrelated to the disease." Paragraph bridging pages 411-412.

Hu's use of the terms "biologically relevant," "relevant to the study" and "biologically meaningful" would encompass diagnostic relevance because a gene whose modest change in expression is unrelated to the disease cannot be used as a tumor marker. The specification only presents data showing a relative difference in PRO1753 mRNA levels. There is no evidence that PRO1753 mRNA was highly expressed. Hu's findings are supported by Wang (Trends Pharmacol Sci. 1996 Aug;17(8):276-9), which teaches that differential display is the first of many steps required in the discovery of a novel pharmacological target, especially given that the function of the factor is most likely unknown. Therefore, further action should be taken to characterize the functions of a particular gene of interest, including ... validation for the importance of the gene in disease processes. See page 279, column 2, full paragraph 1.

The countervailing evidence also shows that the skilled artisan would not know if or how expression of the PRO1753 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. See Haynes (Electrophoresis. 1998 Aug;19(11):1862-71):

> "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" (page 1863, right column, full paragraph 2);

This conclusion is supported by:

Hancock (J Proteome Res. 2004 Jul-Aug;3(4):685):

> "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling" (full paragraph 2);

Molecular Biology of the Cell, 3rd ed. (Exhibit 7, filed 05/02/2005):

> "other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made" (page 435, last full paragraph);

Molecular Biology of the Cell, 4th ed. (Exhibit 8, filed 05/02/2005):

> "the final level of a properly folded protein in a cell therefore depends upon the efficiency with which each of the many steps [from DNA to protein] is performed" (page 363, last full paragraph and page 364, Figure 6-90);

Genes VI (Exhibit 9, filed 05/02/2005):

> "production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848).

the declaration of Dr. Polakis under 37 CFR 1.132 (Exhibit 6, filed 05/02/2005):

> "... there have been published reports of genes for which such a correlation does not exist, ..." (paragraph 6); and,

Meric (Mol Cancer Ther. 2002 Sep;1(11):971-9 (Exhibit 11, filed 05/02/2005):

> Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability. Page 971, left column, first paragraph of introduction.

Even if one were to assume that the disclosed change in PRO1753 transcripts could reasonably be correlated with an assumed change in PRO1753 polypeptide expression the skilled artisan still would not know if the assumed change in PRO1753 polypeptide expression is tumor-dependent or tumor-independent because the skilled artisan would not know if the disclosed change in PRO1753 transcripts is tumor-dependent or tumor-independent.

Finally, one skilled in the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins this classification is insufficient to establish a function or biological significance for the protein because ancient duplications and

rearrangements of protein-coding segments have resulted in complex gene family relationships. Duplications can be tandem or dispersed and can involve entire coding regions or modules that correspond to folded protein domains. As a result, gene products may acquire new specificities, altered recognition properties, or modified functions. Extreme proliferation of some families within an organism, perhaps at the expense of other families, may correspond to functional innovations during evolution. See Henikoff (Science. 1997 Oct 24;278(5338):609-14), page 609, Abstract. Accordingly, one skilled in the art would not accept mere homology as establishing a function of protein because gene products may acquire new specificities, altered recognition properties, or modified functions. Rather, homology complements experimental data accumulated for the homologous protein in understanding the homologous protein's biological role. Although, the presence of a protein module in a protein of interest adds potential insight into its function and guides experiments, insight into the biological function of a protein cannot be automated. However, homology can be used to guide further research. See Henikoff (Science. 1997 Oct 24;278(5338):609-14), paragraph bridging pages 613-614, through page 614, paragraph bridging columns 1-2. Applicants are not relying on homology to establish utility of the PRO1753 polypeptide. Therefore, Henikoff is not germane to the asserted cancer diagnostics and therapeutics of the PRO1753 polypeptide insofar as Applicants are relying solely on the differential analysis of the PRO1753 mRNA expression for utility of the PRO1753 polypeptide. Nevertheless, Figure 110 shows various putative domains of SEQ ID NO: 110, and Henikoff provides evidence that one skilled in the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins this classification is insufficient to establish a function or biological significance for the protein.

The countervailing evidence shows that a skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide because the specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The specification lacks a sufficient correlation between the test performed on PRO1753 mRNA expression and the asserted utility of the PRO1753 polynucleotide, polypeptide and antibodies. In the present case, the asserted diagnostic or therapeutic utilities of the PRO1753 gene, polypeptide and antibodies would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use because the skilled artisan would not know if the reported change in PRO1753 mRNA expression was tumor-dependent or tumor-independent and would not know if or how PRO1753 polypeptide expression would change in tumors. Therefore, the disclosure that DNA68883-1691 is more highly expressed in esophageal tumor as compared to normal esophagus does not impute a specific, substantial, and credible utility to the PRO1753 polypeptide. Regarding the requirement for further experimentation as a basis for lack of utility, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities (M.P.E.P. § 2107.01 I). In the absence of any information on the role, activity, or expression of the PRO1753 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

The disclosure is simply a starting point for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

(10)(a) Response to Argument

Appellants' discussion of the utility legal standard is acknowledged. However, adopting Appellants' standard for utility would result in a per se rule that any disclosed difference in mRNA expression is significant, relevant, and tumor-dependent and that any such difference would require a per se rule of utility for the polynucleotide, the encoded polypeptide and antibodies thereto. The examiner declines to attenuate the utility requirement to this degree because this standard is not what the art teaches. The specification only presents data showing a relative difference in PRO1753 mRNA levels. There is no evidence that PRO1753 mRNA was highly expressed. The countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO1753 transcripts is tumor-dependent or tumor-independent. See Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12). A tumor-independent detection of a change in mRNA expression cannot be used as a tumor marker. The countervailing evidence also shows that the skilled artisan would not know if or how expression of the PRO1753 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation,

processing and modification, which are only apparent by direct protein analysis. See Haynes (Electrophoresis. 1998 Aug;19(11):1862-71), Hancock (J Proteome Res. 2004 Jul-Aug;3(4):685), Molecular Biology of the Cell, 4th ed. (Exhibit 8, filed 05/02/2005), Genes VI (Exhibit 9, filed 05/02/2005), the declaration of Dr. Polakis under 37 CFR 1.132 (Exhibit 6, filed 05/02/2005) and Meric (Mol Cancer Ther. 2002 Sep;1(11):971-9 (Exhibit 11, filed 05/02/2005). Even if one were to assume that the disclosed change in PRO1753 transcripts could reasonably be correlated with an assumed change in PRO1753 polypeptide expression the skilled artisan still would not know if the assumed change in PRO1753 polypeptide expression is tumor-dependent or tumor-independent because it is unknown if the disclosed change in PRO1753 transcripts is tumor-dependent or tumor-independent.

Neither the specification nor any of Appellants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO1753 polypeptide expression changes in tumor tissue. Instead, Appellants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO1753 transcripts and PRO1753 polypeptide expression to argue that it is more likely than not that a change in PRO1753 transcripts is correlated with an assumed change in PRO1753 polypeptide expression. Without any evidence of the expression of PRO1753 in tumor tissue this argument is of no avail to Appellants. A commonly understood general rule or dogma amounts to a showing that it is "not implausible" that invention will work for its intended purpose, which, in the face of the countervailing evidence, is insubstantial evidence of utility for the PRO1753 polypeptide. The inherent lack of certainty in this general correlation results in a failure to prove practical utility for the PRO1753 polypeptide and antibodies.

Because Appellants have failed to validate the significance of PRO1753 gene expression to tumors and have failed to establish the correlation between PRO1753 mRNA expression and PRO1753 polypeptide expression in tumors, Appellants have failed to establish a significant probability that the PRO1753 polypeptide and antibodies are useful as a cancer diagnostic or therapeutic. The specification lacks a sufficient correlation between the test performed on PRO1753 mRNA expression and the asserted utility of the PRO1753 polynucleotide and polypeptide. There is no reason for the skilled artisan to believe that it is more likely than not that the PRO1753 polypeptide and antibodies could be used as a cancer diagnostic or therapeutic. The asserted utility of the PRO1753 polypeptide and antibodies would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Regarding the requirement for further experimentation as a basis for lack of utility, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities (M.P.E.P. § 2107.01 I). In the present case, the asserted diagnostic or therapeutic utilities of the PRO1753 gene, polypeptide and antibodies would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use because the skilled artisan would not know if or how PRO1753 polypeptide expression would change in tumors.

Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Appellants have not provided any testing of the expression of the PRO1753 polypeptide. In the

absence of any information on the role, activity, or expression of the PRO1753 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if the reported change in PRO1753 transcripts is tumor-dependent or tumor-independent and would not know if or how PRO1753 polypeptide expression would change in cancer. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

Appellants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, Appellants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in *Brenner v. Manson*:

> But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO1753 transcripts is tumor-dependent or tumor-independent and would not know if or how expression of the PRO1753 polypeptide would change in tumors.

The examiner concludes that Appellants have failed to disclose how to use the claimed invention.

Appellants argue that the examiner has failed to establish a prima facie showing that a skilled artisan would reasonably doubt the asserted utility because the data in example 18 are sufficient to establish utility. In this regard appellants refer a declaration of Christopher Grimaldi (Exhibit 1, filed 05/02/2005). Appellants further argue that only the relative level of expression is important and that how high the level of expression is, is irrelevant. Appellants' arguments have been fully considered but they are not persuasive.

The declaration of Christopher Grimaldi (Exhibit 1, filed 05/02/2005) has been considered. However, the assertions that "Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual" (paragraph 5), "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA" (paragraph 6), "The precise levels of gene expression are irrelevant" (paragraph 7), and "If a difference is detected, ... the gene and its corresponding polypeptide ... are useful for diagnostic purposes" (paragraph 7) are conclusory and unsupported. Furthermore, the declaration does not provide any data concerning PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. Contrary to appellants' assertion that how high the level of expression is, is irrelevant, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. See Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12. A gene whose change in expression is due to disease-independent differences between samples cannot be used as a diagnostic marker of the disease.

Given the paucity of information regarding PRO1753 mRNA expression and the complete lack of data concerning PRO1753 polypeptide expression, Hu is evidence that a skilled artisan would regard the precise level of PRO1753 mRNA expression as relevant.

Regarding the Grimaldi declaration (Exhibit 1, filed 05/02/2005), Appellants argue that the examiner should accept Mr. Grimaldi's opinion. This has been fully considered but is not found to be persuasive. In the instant case, the nature of the facts to be established are whether or not the change in PRO1753 transcripts is related to the disease or unrelated to the disease, whether or not there is a correlation between a change in PRO1753 transcripts and PRO1753 polypeptide expression in tumors, and if so, whether such a correlation could be used as a cancer diagnostic. The skilled artisan would not know if the results seen in Example 18 were disease-dependent or disease-independent. Appellants have not provided any testing of the expression, role, or activity of the PRO1753 polypeptide. Even if the examiner were to assume that the present results with PRO1753 transcripts could reasonably be correlated with an assumed change in PRO1753 polypeptide expression, it still could not be ascertained if the assumed change in PRO1753 polypeptide expression would be disease-dependent or disease-independent because one would not know if the change in PRO1753 transcripts is disease-dependent or disease-independent.

Appellants argue that Hu's results reflect a bias in the literature and reflect nothing regarding the ability of gene that is at least 2-fold differentially expressed to serve as a disease marker. Appellants argue that Hu's methodology provides little or no information regarding the ability of genes with less than a 5-fold difference in expression to serve as a disease marker. Appellants argue that Hu does not refute, and cannot be used to refute, the asserted diagnostic

utility of the PRO1753 polypeptide. Appellants' arguments have been fully considered but they are not persuasive. Hu's use of the term "biologically relevant," "biologically meaningful," or "relevant to the study" would encompass diagnostic relevance because a gene whose change in expression is unrelated to the disease cannot be used as a diagnostic indicator of the disease. Hu's results indicate that a skilled artisan would not know if a 5-fold or less difference in expression was tumor-dependent or tumor-independent. There is no evidence of record that a change in PRO1753 mRNA or polypeptide expression is tumor-dependent, consistent and measurable. Therefore, Hu's results indicate that a skilled artisan would not know if the reported change in PRO1753 transcripts was tumor-dependent or tumor-independent.

Although Hu indicates that the observed correlation was only found among ER-positive tumors, not ER-negative, Hu's approach identified a set of relatively understudied, yet highly expressed genes in ER-negative tumors that are worthy of further examination. This is consistent with Hu's conclusion that even when expression changes as small as 2-fold are statistically significant, it is not always clear if they are biologically meaningful. These small changes in expression may reflect genes whose role in cancer may not involve large changes in expression or genes whose modest changes in expression may be unrelated to the disease.

Appellants assert that it is the examiner's position that one must know what role a gene or polypeptide plays in cancer in order for it to have utility. Appellants misstate the examiner's position. It is the examiner's position that Appellants have not provided any information regarding the role, expression or activity of the PRO1753 polypeptide in cancer. The examiner is not saying that Appellants must disclose the activity or role in cancer of the PRO1753

polypeptide. The examiner is saying that Appellants have not provided any information in the regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide.

Appellants argue that the PTO cannot rely on Wang to require that appellants provide polypeptide expression data. Appellants' arguments have been fully considered but they are not persuasive. Appellants were the ones that argued that they have completed the equivalent of steps 1-9 of the ten steps outlined by Wang in Figure 1. The examiner disagreed with this assertion because the specification does not provide any information regarding the target validation of the PRO1753 polypeptide. The specification does not establish if or how PRO1753 polypeptide expression changes in tumors. The lack of utility for the PRO1753 polypeptide remains because the skilled artisan would not know if the observed change in the PRO1753 transcript is disease-dependent or disease-independent and would not know if or how PRO1753 polypeptide expression changes in tumors. Appellants have not validated the importance of PRO1753 gene or polypeptide expression to the disease process, from either a diagnostic or pharmaceutical viewpoint. A gene whose change in expression is unrelated to the tumor cannot be used as a diagnostic marker for the tumor.

Appellants emphasize that neither Haynes not Gygi looked at whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Appellants argue that neither Haynes nor Gygi provide any insight into the affects on protein level caused by a change in the encoding mRNA level. Appellants' arguments have been fully considered but they are not persuasive. The examiner emphasizes that appellants have not looked at whether the reported change in the transcript level for the PRO1753 gene leads to a change in the level of expression of the PRO1753 polypeptide. It is

further noted that appellants' differential analysis is based upon comparing the steady-state levels of PRO transcripts in one or more normal tissues with the steady state levels of PRO transcripts in one or more tumor tissues. See the specification at page 140, paragraph 0530:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor.

Appellants assume that PRO1753 transcript levels are indicative PRO1753 polypeptide levels. In effect, Appellants' position is that PRO1753 transcript levels are the sole determinant of PRO1753 levels. The specification fails to provide any testing of PRO1753 polypeptide levels.

Haynes (Electrophoresis. 1998 Aug;19(11):1862-71) states:

> "Interpretation of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression" (page 1863, left column, full paragraph 1),

Haynes goes on to state:

> "These results suggest that even for a population of genes predicted to be relatively homogenous ..., the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (page 1863, left column, full paragraph 1).

Haynes concludes that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript. Haynes provides evidence that protein expression levels are not predictable from the mRNA expression levels. Haynes cites this lack of predictability as one of the main reasons for proteome analysis to become an essential component in the

comprehensive analysis of biological systems. Paragraph bridging pages 1862-1863; page 1863, left column, full paragraph 1. Haynes further teaches:

> "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" (page 1863, right column, full paragraph 2).

Because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis the skilled artisan would not know if the disclosed change in PRO1753 mRNA transcripts is associated with a corresponding change in the level of PRO1753 protein. Hence, the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer. This conclusion is supported by Haynes, Hancock, Molecular Biology of the Cell, 4th ed. (Exhibit 8, filed 05/02/2005), Genes VI (Exhibit 9, filed 05/02/2005), the declaration of Dr. Polakis under 37 CFR 1.132 (Exhibit 6, filed 05/02/2005) and Meric (Exhibit 11, filed 05/02/2005), as discussed above.

Appellants argue that Hancock does not support the PTO's position because Hancock is arguing that proteomics has not developed sufficiently to be a reliable method of generating biomarkers. Appellants' arguments have been fully considered but they are not persuasive. Regarding the shortcomings of proteomic methods, Hancock is speaking of the push to validate currently available biomarkers in an extensive clinical setting:

> The Editor has become aware of a recent push to validate currently available biomarkers in an extensive clinical setting. ... The challenge in this situation is to balance the need of patients for better, early diagnosis of disease with the need to have high-quality markers for the expensive and time-consuming validation process. This Editor believes that proteomics is at too early a stage for this new technology to have generated a quality list of markers.

Hancock's teaching that "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling" is as applicable to the use of expression profiling and proteomics to generate additional markers as it is to their use at the clinical stage. Hancock is evidence that a situation, such as the present one, wherein only a change in transcripts is presented, is a situation that would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use for the polypeptide. The specification lacks a sufficient correlation between the test performed on PRO1753 mRNA expression and the asserted utility of the claimed polypeptides.

Appellants argue that it is more likely than not that the PRO1753 polypeptide is differentially expressed, as supported by the Grimaldi declaration (Exhibit 5, filed 05/02/2005) and the Polakis declaration (Exhibit 6, filed 05/02/2005), as supported by the Molecular Biology of the Cell, 3rd ed. (Exhibit 7, filed 05/02/2005) and Molecular Biology of the Cell , 4th ed. (Exhibit 8, filed 05/02/2005), as further supported by Genes VI (Exhibit 9, filed 05/02/2005) and as additionally supported by Zhigang (Exhibit 10, filed 05/02/2005) and Meric (Exhibit 11, filed 05/02/2005). Appellants' arguments have been fully considered but they are not persuasive.

The Grimaldi declaration (Exhibit 5, filed 05/02/2005) has been considered. However, the facts to be established are whether or not the disclosed change in PRO1753 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO1753 transcripts and a change in PRO1753 polypeptides levels in tumors as compared to their normal tissue counterparts. In the present case it is unknown if the reported differences in PRO1753 mRNA expression are tumor-dependent or tumor-independent. The declaration does not provide any data concerning PRO1753 mRNA expression, PRO1753

polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by Hancock (J Proteome Res. 2004 Jul-Aug;3(4):685) and the declaration of Dr. Polakis under 37 CFR 1.132 (Exhibit 6, filed 05/02/2005). The assertion that PRO1753 polypeptide expression is useful regardless of the correlation between PRO1753 mRNA expression and PRO1753 polypeptide expression because it would allow more accurate tumor classification is akin to asserting that whatever the expression level and whatever the correlation, the PRO1753 polypeptide and antibodies are useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding "more accurate tumor classification." The examiner does not agree that such a disclosure provides a "specific benefit in currently available form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect, characterize or classify the tumor. Such an asserted utility is not specific to the PRO1753 gene or polypeptide and is analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility.

The Polakis declaration (Exhibit 6, filed 05/02/2005) has been considered. However, the facts to be established are whether or not the disclosed change in PRO1753 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO1753 transcripts and a change in PRO1753 polypeptides levels in tumors as compared to their normal tissue counterparts. The declaration does not provide any data concerning PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. There is no evidence of record that either the PRO1753 polynucleotide or the PRO1753 polypeptide were abundantly expressed. The specification does not teach the level of reproducibility or reliability of the results seen in Example 18. Given the paucity of information regarding PRO1753 expression in tumors and the evidence in the art that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would not know if the change in PRO1753 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO1753 polypeptide expression would change in tumors, and would have a reasonable, legitimate basis to doubt the utility of the PRO1753 polypeptide. Even if the examiner were to assume that the disclosed change in PRO1753 transcripts could reasonably be correlated with an assumed change in PRO1753 polypeptide expression, it still could not be ascertained if the assumed change in PRO1753 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO1753 transcripts is disease-dependent or disease-independent. While Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. No data or results were presented for independent analysis. Even if the examiner were to accept Dr. Polakis'

conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to Dr. Polakis. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis.

Molecular Biology of the Cell, 3rd ed. (Exhibit 7, filed 05/02/2005), Molecular Biology of the Cell, 4th ed. (Exhibit 8, filed 05/02/2005), Genes VI (Exhibit 9, filed 05/02/2005), Zhigang (Exhibit 10, filed 05/02/2005) and Meric (Exhibit 11, filed 05/02/2005) are acknowledged. However, none of this evidence provides any data concerning PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. Molecular Biology of the Cell, 3rd ed. (Exhibit 7, filed 05/02/2005) teaches that other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made (page 435, last full paragraph). Molecular Biology of the Cell, 4th ed. (Exhibit 8, filed 05/02/2005) acknowledges that the final level of protein depends upon the efficiency with which each of the many steps from DNA to protein is performed (page 363, last full paragraph and page 364, Figure 6-90). Genes VI (Exhibit 9, filed 05/02/2005) acknowledges that "production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848). Molecular Biology of the Cell and Genes VI support and are consistent with the examiner's position that the skilled artisan would not know if or how

PRO1753 polypeptide expression would change in cancer and that the application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The examiner does not agree that Figure 6-3, page 302 (Exhibit 8, filed 05/02/2005) illustrates a basic principle that there is a correlation between increased gene expression and increased protein expression. This figure only illustrates that different genes can be expressed with different efficiencies.

It is acknowledged that Zhigang (Exhibit 10, filed 05/02/2005) presents data showing a high degree of correlation between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence). However, exceptions were noted (paragraph bridging pages 3 of 7 and 4 of 7; page 4 of 7, left column, full paragraph 1), and unlike Zhigang, appellants have not provided any testing of PRO1753 polypeptide expression. The application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Further experimentation would be required in order to identify or reasonably confirm a "real world" context of use.

It is acknowledged that Meric (Exhibit 11, filed 05/02/2005) states that the "fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells" (page 971, right column, first paragraph of "Introduction"). However, the specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO1753 polypeptide. Therefore, the difference in PRO1753 polypeptide expression between cancer cells and normal cells is unknown, and thus not exploitable. Meric also acknowledges that several alterations in translational control occur in cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right

column, first paragraph of "Introduction"), suggesting that protein levels can be modulated independently of the level of mRNA. Thus, Meric supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer and that the application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Appellants argue that Meric does not detail the relationship between differential mRNA levels and changes in protein levels. However, the specification also does not detail the relationship between differential PRO1753 mRNA levels and changes in PRO1753 protein levels. The examiner is not arguing that the techniques that measure gene levels, such as microarray analysis, differential display, and quantitative PCR, are without merit. The examiner is arguing that Appellants have failed to establish the correlation between a change in PRO1753 mRNA expression and a change, if any, in PRO1753 polypeptide expression.

The examiner does not agree that the caveat in Example 12 of the utility guidelines is applicable to the present situation because unlike the situation wherein the specification discloses that receptor A is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells, in the present case Appellants rely on a qualitative comparison of PRO1753 mRNA expression between tumor tissue and normal samples in order to establish utility for the claimed polypeptides. However, the specification does not teach the level of reproducibility or the level of reliability of the results seen in Example 18. The skilled artisan would not know if this difference is disease-dependent or disease-independent. Furthermore, Appellants have not provided any testing of the expression, role, or activity of the PRO1753 polypeptide. Even if the examiner were to assume that the change in PRO1753 mRNA

transcripts could reasonably be correlated with a change in PRO1753 polypeptide expression, it still could not be ascertained if the assumed change in PRO1753 polypeptide expression would be disease-dependent or disease-independent because the skilled artisan would not know if the change in PRO1753 transcripts is disease-dependent or disease-independent. The specification lacks a sufficient correlation between the test performed on PRO1753 transcripts and the asserted utility of the claimed polypeptides. Because Appellants have failed to establish any correlation between PRO1753 mRNA expression and PRO1753 polypeptide expression in normal tissue and tumor tissue, Appellants have failed to establish a significant probability that PRO1753 polypeptide is useful as a cancer diagnostic or therapeutic. There is no reason for the skilled artisan to believe that it is more likely than not that the claimed polypeptides could be used as a cancer diagnostic or therapeutic.

Appellants' conclusion regarding the utility of the claimed invention has been considered but it is not persuasive. In the present case, the differential analysis of PRO1753 transcripts does not prove that the PRO1753 polypeptide will perform as a cancer diagnostic or therapeutic. The differential expression of the PRO1753 polynucleotide has not been adequately correlated with the contemplated cancer diagnostics or therapeutics of the PRO1753 polypeptide or antibodies. The PRO1753 polynucleotide and polypeptide have not been tested to the extent that utility would be known to those of skill in the art.

(9)(b) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 6-8 and 11-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10)(b) Response to Argument

Appellants argue that they have established a substantial, specific, and credible utility for the claimed polypeptides. Appellants' arguments have been fully considered but they are not persuasive. As Appellants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

(9)(c) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 14-17 recite the limitation "wherein said polypeptide ... can be used to generate an antibody ... ." These claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity. To obtain a valid patent, a patent application must be filed that contains a full and clear disclosure of the invention in the manner prescribed by 35 U.S.C. 112, first paragraph. The requirement for an adequate disclosure ensures that the public receives something in return for the exclusionary rights that are granted to the inventor by a patent. If mere antigenic cross-reactivity were the test for enablement under § 112, Appellants could obtain patent rights that may confer power to block off whole areas of scientific development related to the biologic activity of the polypeptide, for which Appellants have not provided any disclosure. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO1753, which is ideally suited to the making of antibodies to itself, would enable any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification provides no disclosure of any biological activity. Therefore, the scope of enablement provided to the skilled artisan by the disclosure is not commensurate with the scope of protection sought by the claims.

(10)(c) Response to Argument

Appellants argue that the examiner has failed to establish a prima facie case for rejecting claims 14-17 as lacking enablement because the standard for enablement is based on undue experimentation.

Appellants argue that the examiner failed to make any specific findings of fact.

Appellants argue that the power to block off whole areas of scientific development is not the test for enablement.

Appellants argue that disclosure of a biological activity is not required for a skilled artisan to make or use the claimed polypeptides.

Appellants argue that disclosure of a single polypeptide cannot support a rejection for lack of enablement.

Appellants argue that the specification teaches how to make the claimed polypeptides and antibodies that bind thereto. Appellants argue that the specification provides sufficient guidance as to how to use the claimed polypeptides.

Appellants' arguments have been fully considered but they are not persuasive. All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:

> "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the

> ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 110, and possessing any and/or all underlying biological activities. The level of experimentation required to make and use such an invention is clearly beyond the level of enablement provided by the specification because the specification provides no disclosure of any biological activity of the native or naturally-occurring PRO1753 polypeptide SEQ ID NO: 110.

Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal samples is essential to appellants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. The level of ingenuity required to make such an invention is clearly beyond that to be expected of skilled artisans. The specification does not disclose how this would be accomplished. Note that the claims are not limited to fusion proteins. Rather the claims encompass polypeptides that vary anywhere and everywhere from SEQ ID NO: 110, within the metes and bounds of the recited percent identity.

The examiner has provided sufficient evidence and reasoning to make a prima facie showing that appellants' disclosure is not commensurate in scope with the claimed invention, which requires antibodies that "specifically detect the polypeptide of SEQ ID NO: 110."

Appellants separately argue that claim 15 is enabled for the same reasons that claims 14, 16 and 17 are enabled. Appellants further argue that the scope of claim 15 is narrower than that of claim 14, and thus less experimentation will be required to make these polypeptides. Appellants argue that a skilled artisan would clearly be able to use these polypeptides. Appellants' arguments have been fully considered but they are not persuasive. Claim 15 is not enabled for the same reasons claim 14 is not enabled, as discussed above. Although the polypeptides of claim 15 are 99% identical to SEQ ID NO: 110, the level of experimentation required to make and use such an invention is still clearly beyond the level of enablement provided by the specification because the specification provides no disclosure of any biological activity. Furthermore, the state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant.

(9)(d) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity. Appellants have not described the biologic activity of the PRO1753 polypeptide or any of its variants. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO1753, which is ideally suited to the making of antibodies to itself, would describe any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification does not describe any biological activity. Therefore, the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(10)(d) Response to Argument

Appellants argue that the examiner has not provided any reasoning or evidence as to how the absence of the disclosure of a biological activity results in a lack of written description.

Appellants argue that there is no substantial variation within the genus and that appellants were in possession of the common attributes or features of the claimed invention.

Appellants argue that the claims are analogous to Example 14 of the written description guidelines because it was well known in the art how to make polypeptides having the recited percent identity, as evidenced by the specification at paragraphs 0256-0271, and because the specification discloses how to make antibodies that detect a particular PRO polypeptide and how to use them, as evidenced by the specification at paragraphs 0363-0379, 0407 and 0493-0499. Appellants argue that the function of producing an antibody specific to SEQ ID NO: 110 is directly related to the structure of the claimed polypeptides. Appellants argue that example 14 of

the written description guidelines extends to all situations where the polypeptide is useful and there is no substantial variation within the genus. Appellants argue that claims 14-17 must share a particular biologic activity which restricts the amount of permissible structural variation within the genus.

Appellants argue that the premise that a large genus cannot be described by a single species is wrong. Appellants argue that it is routine to make the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. Appellants argue that it well within the purview of skilled artisans to determine which polypeptides can be used to make the recited antibodies. Appellants argue that the predictability of this structure/function combination is sufficient to put appellants in possession of the claimed invention.

Appellants' arguments have been fully considered but they are not persuasive.

The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:

> "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 110, and possessing any

and/or all underlying biological activities. However, the specification does not describe any biological activity of the native or naturally-occurring PRO1753 polypeptide SEQ ID NO: 110.

The examiner disagrees with the premise that making the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. All nucleic acid molecules that encode a particular amino acid sequence all share the same property of encoding that amino acid sequence. The nature, type and number of nucleotide changes are discernable and predictable. However, the claimed variant polypeptides are all different polypeptides. The claims encompass polypeptides that vary anywhere and everywhere from SEQ ID NO: 110, within the metes and bounds of the recited percent identity. Note that the claims are not limited to fusion proteins. Unlike a biological activity, which imposes limitations on the nature, type and number of amino acid changes, the functional property of "can be used to generate an antibody ... to specially detect the polypeptide of SEQ ID NO: 110" does not limit the variation in the structure SEQ ID NO: 110 —the structure of the claimed variants — in any discernable, predictable or disclosed manner. Because the specification does not describe any biological activity of the claimed polypeptides and because the claims are not limited to any specific biologic activity of the claimed polypeptides, the present claims are not analogous to example 14 of the written description guidelines.

Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal samples is essential to appellants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. Therefore, the function of the claimed variants is not related to the structure of the claimed variants. Therefore, skilled artisans would not recognize the disclosure of SEQ ID NO: 110 as putting appellants in possession of the claimed genus.

Appellants separately argue that claim 15 is adequately described for the same reasons that claims 14, 16 and 17 are adequately described. Appellants further argue that because the genus of polypeptides is smaller than that of claim 14 the board should reverse the rejection of claim 15. Appellants' arguments have been fully considered but they are not persuasive. Claim 15 is not adequately described for the same reasons claim 14 is not adequately described, as discussed above. Although the polypeptides of claim 15 are 99% identical to SEQ ID NO: 110, the specification does not describe any biological activity of the native or naturally-occurring PRO1753 polypeptide SEQ ID NO: 110 or any variant thereof. Furthermore, the state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. Skilled artisans would not

recognize the disclosure of SEQ ID NO: 110 as putting appellants in possession of the claimed genus.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Non-Appealable Issues

Regarding "APPENDIX B – Evidence" of the Appeal Brief and for clarity of the record, it is noted that Gygi et al. (Mol Cell Biol. 1999 Mar;19(3):1720-30) was first submitted by Appellants as Exhibit 4 on 05/02/2005.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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